UNIT FOUR TEACHER BACKGROUND INFORMATION

Unit overview

Understanding how the immune system functions, is very important for our health. The immune system is our protection from invading molecules, pathogens, cancer, and viruses. How our immune system can be tuned to recognize almost any possible invader while sparing our own cells gives us an incredible cellular and molecular tool to fight infections and diseases. The study of the molecular and cellular components that comprise the immune system, including their function and interaction, is immunology. The immune system is divided into a more primitive innate immune system, and an acquired or adaptive immune system (in vertebrates) which contains **humoral** and cellular components.

This unit gives an overview of the immune system through exploring the developmental pathways of the hematopoietic stem cell. Discussing the functions of blood stem cell descendents and several disorders that afflict them will give students a greater understanding of the immune system in human health and medicine. Teachers may wish to open with asking students to list how the immune system can be both a promising avenue for research and an obstacle for cures. Our immunity is perhaps the most important resistance against infectious diseases, and may in the future be enhanced or adjusted so it does not react to **allogeneic** transplants. The immune system makes us reject organ or cell transplants that would help us get better. It reacts with artificial bone and joint replacements. It must be suppressed or somehow overcome with an **allogeneic** transplant (one from another), because an **autologous** transplant (one to yourself) is not always possible. Hematopoietic stem cell research has and may yield treatments for serious blood diseases and increase the availability and diversity of tissue for transplants.

In this review, a discussion of blood cell development will be presented-first, to understand the origination of blood and the diversity of cell types. Second, to understand acquired and innate immunity along with functions of white blood cells. Third, to understand diseases of the blood and immune system. Students will learn about these disorders and how to diagnose them through case studies and a web project.

Before beginning this unit, it would be helpful for students to have already learned about the functions of red blood cells in the circulatory system, which can be found here http://www.umm.edu/blood/blood.htm.

Invite your students to think about how white blood cells differ from red blood cells, then play "The Cell is Right" to help them understand the origins of all types of blood cells. In this unit, you may discuss any of the following: the origins of the blood/immune system; the "lineage tree" members and their organization and functions; the genetic and environmental causes of sickness; the molecular mechanics, disease progressions, and physical symptoms of leukemia, lymphoma, sickle cell anemia, and AIDS; bone marrow transplants and uses of hematopoietic stem cells to treat these disorders- immunocompatibility, tissue typing, rejection.

Origins
Hematopoietic (from Ancient Greek: *haima* blood; *poiesis* to make) or blood-forming stem cells are at the root of an extensive blood differentiation lineage tree, giving rise to the complete blood system. This complex system—consisting of the **Erythroid**, **Lymphoid**, and **Myeloid** branches—1) performs oxygen-delivery and carbon-dioxide removal from all your body's tissues and 2) is your body's defense against intrinsically and extrinsically caused damage, disease, infection, and cancer.

Development
Hematopoietic stem cells originate in **blood islands** that develop near the yolk end of the 3 week embryo. The first blood cells formed are red blood cells, or **erythrocytes**. Because at this stage passive diffusion of oxygen is insufficient to sustain the embryo, a red blood cell delivery system develops. In the beginning developmental stages of the primitive circulatory system, a network of vessels forms from **hemangioblasts**, stem cells that can form blood cells and vessel cells. Tubular vessels take shape, and along their inner lining (surrounding the lumen), multinucleated masses (blood islands) incubate **reticulocytes** (immature RBCs) which then acquire hemoglobin and bud off. Until the 8th week of development these primitive nucleated erythroid cells are found in the yolk sac; they contain hemoglobin but don't mature to fully developed RBCs. At about 6 weeks of development, blood islands begin to regress as **hematopoiesis** migrates to the liver. At 8 or 9 weeks hematopoietic stem cells are detectible in the liver and they begin to proliferate. Granulocytes also appear in the liver during the 2nd month. The spleen also contributes to hematopoiesis at this point. During the 4th month hematopoiesis begins in the bone marrow, and by the 5th month this becomes the primary site of blood cell production. Differentiation of hematopoietic stem cells down all lineages occurs during gestation and continues throughout adulthood.

The Hematopoietic stem cell "lineage tree"
Multipotency is the inherently controlled yet extrinsically regulated ability of a cell to differentiate into multiple cell types. A human hematopoietic stem cell has the most extensive linage tree as compared to other adult multipotent cell types, and can ultimately differentiate into at least 11 terminally differentiated cell types (not shown in the figure below). The developmental "choices" of hematopoietic stem cells include the **Lymphoid** branch, containing common lymphoid stem cells and progenitors that mature in the spleen, thymus, and lymph nodes (lymphatic system) and give rise to **T-cells** and **B-cells**, white blood cells that enforce nonspecific and specific immunity; and the **Myeloid** branch, in which myeloid stem and progenitor cells give rise to the **granulocytes**, **megakaryocytes**/**platelets**, **dendritic** cells, and **macrophages** which participate in both types of immune response. The myeloid branch also generates the **Erythroid** lineage, containing **reticulocyte** (immature) and **erythrocyte** (mature) red blood cells.

Simplified Hematopoietic (blood) stem cell tree. See Unit Four Appendix B lineage tree All adult blood cells originate from HSCs (blood stem cells) in the bone marrow. © 2007 Terese Winslow, U.S. Govt. has certain rights Each branch (lymphoid, myeloid, and erythroid) serves a unique overall functional purpose but work in concert to achieve elimination or containment of infectious organisms. (AP extension question: *How do their purposes overlap?*) In the above diagram, the erythroid branch is represented by an arrow from the myeloid stem cell to the red blood cells. Derived from myeloid stem cells, **platelets** are a vital part of the coagulation process whereby the body plugs and fixes blood vessel leaks.

The Lymphoid Branch
The Lymphoid branch has **lymphatic leukocytes** (from *leukos* white; and *kytos* cell) that work together to destroy foreign organisms based on recognition of specific, individual "*microtags,*" or **antigens** comprised of a tiny portion of the "invaders." **Antigen presenting cells (APCs)**, mainly macrophages and dendritic cells eat and process invaders and display them on their cell surface to elicit responses from leukocytes. Before an immature white blood cell reaches its final functional state, it must mature in specific organs throughout the body. Along the Lymphoid lineage, functional differentiation happens in two stages. First, B-cells and T-cells are produced in the bone marrow. In the bone marrow, B-cells mature to the point at which they can recognize antigens (you can remember them because they *mature* in the Bone marrow.) Immature T-cells differentiate into their "naïve" state, through maturation in the Thymus. Naïve in this context means they have not had exposure antigen. B and T cells become fully mature *after* they come in contact with antigens, and can then further differentiate into subtypes of B and T cells with even more specialized functions. A mysterious class of

lymphocytes—Natural Killer cells—are thought to recognize and destroy tumor cells and some virally-infected cells through a self/non-self recognition process.

The Myeloid Branch
The Myeloid branch has **non-lymphatic** or **myelogenous leukocytes** that generally recognize and eat/destroy:

a) naturally-dying/dead body cells
b) pieces of damaged or infected tissue
c) bacteria
d) other non-replicative foreign molecules, like biological implants.

These cells can do this because they are capable of innate immunity. This can be thought of as a natural ability to attack and get rid of the invaders *without employing a specific antibody production and recognition mechanism* as with B and T cells. Myelogenous leukocytes are involved in the wound- healing process and act as a cleanup crew. They also have ability to efficiently **phagocytose** (eat) dirt, debris, microorganisms, pieces of damaged or infected tissue and dead cells. Subsets of these cells respond to **inflammatory molecules** and physically migrate through the blood along a biochemical gradient (called **chemotaxis** and **diapedesis**), then enter infected or injured tissues. Neutrophils, monocytes, macrophages, and macrophage-like cells secrete inflammatory mediators and function as **phagocytes** (more about these cells below). Phagocytosis is a form of endocytosis whereby a phagocytic cell engulfs and usually destroys particulate matter. Due to this ability to eat and sample the tissues, they are able to capture antigens from different parts of the body and present this antigen to naïve lymphocytes. Phagocytes, mainly macrophages and dendritic cells, are key in producing a robust adaptive immune response.

The Erythroid Branch
The Erythroid branch has red blood cells ,which transport oxygen to and carbon dioxide from tissues. Immature reticulocytes purge their nuclei during their maturation phase, leaving functional enucleated cells called erythrocytes. Their biconcave shape is the most efficient at oxygen and carbon dioxide exchange, and also aids RBCs in flowing single-file through capillaries.

IMMUNITY
Innate immunity
What is innate immunity?
During an infection, the bone marrow increases its production and release of neutrophils and monocytes. Innate immunity, as mentioned above, is a function of myeloid branch-cells such as **granulocytes** (eosinophils, neutrophils, and basophils), macrophages, and dendritic cells.

Granulocytes- Granulocytes are called this because they contain granules—enclosed packets of inflammatory mediators or toxic chemicals and enzymes that are released to directly destroy their targets.
Eosinophils-Eosinophils, which have granules that look red after staining with Eosin, destroy multicellular parasites and participate in immediate hypersensitivity reactions (allergies).
Neutrophils- Neutrophils (neutral-colored after staining) can undergo phagocytosis to ingest infectious organisms and release vasodilators that allow white blood cells to more easily enter tissues from the blood stream, as well as chemotaxins that attract lymphocytic leukocytes.
Basophils-Basophils, which are identified by their purple-staining granules, carry out functions in *blood* similar to **mast cells** in tissues; they release histamine and other chemicals involved in inflammation as well as heparin, an anticoagulant.
Phagocytic cells
Monocytes give rise to **macrophages**; monocytes travel through the blood stream from their birthplace in the bone marrow, squeeze through the lining of dilated blood vessels to enter tissues, and then differentiate into macrophages. Macrophages are functional, terminally-differentiated cells that phagocytose particulate matter, including microbes. They are found in large numbers along barriers between the body and the external environment, like skin and internal surfaces of respiratory and digestive system tubes. They also secrete antimicrobial chemicals and protein messengers that function as local inflammatory mediators. Macrophages process and present antigen to cytotoxic and T helper cells (mentioned later), and they coordinate systemic responses to infection or injury. Several cell populations scattered in almost all tissues have macrophage-like functions but are not descended from monocytes; these are called **macrophage-like cells** and a specific example is microglia in the central nervous system. Dendritic cells are phagocytic cells that internalize microorganisms to present to lymphocytes and thus induce adaptive immunity. Like macrophages, they survey tissues and ingest dead and infect cells as well as invaders. However, instead of being more degradative like the macrophage, they process and present their cargo to lymphocytes more efficiently than macrophages. Once they encounter a trigger for maturation, they become less phagocytic and migratory. Mature dendritic cells have long processes similar to the dendrites of neurons and are therefore able to make contact with many lymphocytes.

Acquired immunity
Acquired immunity is the body's way of making a "custom fit" immune response to remember a pathogen and elicit a more robust response during subsequent recognitions in a shorter amount of time.

Role of lymphoid cells
Acquired immunity is carried out by cells along the lymphoid branch. Their early

development takes place in the bone marrow. All lymphoid cells are derived from a lymphoid (multipotent) stem cell, which gives rise to lymphoid progenitor cells that either partly differentiate into a **naïve T cells** or mature into B cells.

Lymphoid cells are antigen-specific

Each lymphocyte synthesizes and inserts into its plasma membrane a *single type* of protein **receptor** that can bind to a specific antigen. So, each lymphocyte is specific for just one type of antigen. The antigen receptor is generated through a random and complex but well-characterized genetic rearrangement process. (For an animation of this process, visit <http://www.blink.biz/immunoanimations/index1.html> click *Open*, then *Antigen Recognition*, then *Gene Recombination*. Flash 5 is required to view this and other animations.)

Further maturation of lymphoid cells

At this stage in the bone marrow, B cells are ready to recognize antigen and float through the blood stream into secondary lymphoid organs where they may be **activated** (encounter and respond to corresponding antigen). In contrast, naïve T cells are carried to the Thymus where they mature into helper T cells and cytotoxic T cells, then later undergo cell division in secondary lymphoid organs. *Note:* Emphasize to your students that the above diagram/lineage tree is simplified and in reality B cells and T cells divide and differentiate into classes of cells that all use immunoglobulin cell-surface receptors (helper, cytotoxic, suppressor, and memory T cells as well as mature and memory B cells). Plasma cells produce free-floating immunoglobulins called antibodies that help the body identify and respond to immunogens

Why is acquired immunity important?

Acquired immunity is critical in fighting infections by bacteria, fungi, viruses, parasites, and other environmental factors because an individual may be exposed to these many times throughout the lifespan and it is advantageous to be able to increase the intensity of the immune response. However, highly immunogenic substances also include (but aren't limited to): large molecular weight proteins (above 100,000), polysaccharides, molecules with complex chemical structure, biomaterials used in tissue and organ replacement, and proteins made by different species. Immune responses are in some respects genetic thus immune tendencies can be inherited.

How do T cells know not to attack our own tissues?

A crucial screening process occurs during T cell development. Only T cells that recognize the **class I and II Major Histocompatibility Complex (MHC) proteins** produced by and carried on the plasma membranes of all the host's cells will survive in the thymus or marrow to begin the maturation process. Called **positive selection,** this screening process ensures that mature lymphocytes will attack *only* when antigen from

foreign organisms is presented by MHC proteins but will not attack our own cells—ones containing MHC proteins without foreign antigens. Think of this as an obstacle course for T cells that should result in T cells that only recognize non-self. As T or B cells mature, if they engage self-antigens, they will undergo apoptosis, a form of **negative selection**.

What happens to self-recognizing lymphocytes that slip through the screening process? Any auto-reactive immune cells that escape these selection processes usually become quiescent and inactive. However, through poorly understood mechanisms, the body's own, healthy tissues can be the targets of attack in cases of **autoimmunity**. One autoimmune disorder is severe lupus (*systemic lupus erythematosus*), in which T cells and B cells react to connective tissue in joints, muscles, and skin; the outer covering of the heart; the gastrointestinal tract; the kidneys; the retinas; and the brain—destroying these tissues. Surface proteins on red blood cells and platelets can become reactive, causing lysis of red blood cells and decreased clotting. Lupus can be treated by a bone marrow transplant, discussed later.

STAGES OF THE ACQUIRED IMMUNE RESPONSE

A typical specific immune response has four stages. First, lymphocytic leukocytes encounter and recognize an antigen. Second, antigen binding activates lymphocytes to undergo asymmetric cell division. Third, the lymphocyte daughter cells launch an attack against all antigens identical to the initial activating antigen. Finally, some leftover daughter lymphocytes (memory B and memory T cells) are responsible for memory responses in acquired immunity: the next time these cells encounter the same antigen, which can be years after the initial exposure, they will initiate a stronger and faster immune response. Here are detailed descriptions of these steps from initial encounter through subsequent encounter.

1) Initial encounter/Activation

a. Location: In the Secondary lymphoid organs, lymph nodes, lymph system, blood stream, or in tissues

b. An estimated 100 million distinct antigen receptors have the potential to bind antigen and create progeny called "**clones**." If this lymphocyte later encounters an antigen, the antigen binds to the cell surface receptors. The binding of antigen to receptor must occur for **lymphocyte activation**. When a **B Lymphocyte** detects an **antigen** from a foreign (environmental) source, it does two things. First, it multiplies. Upon binding to an antigen, the lymphocyte undergoes a cell division, then the two resulting daughter cells also divide (even though only one of them still has the antigen attached to it) and so on. So, the original binding of antigen by a single lymphocyte specific for that antigen triggers multiple cycles of

cell divisions (**proliferation**). As a result, many lymphocytes form that are identical to the one that started the cycles and can recognize the antigen; this is termed "clonal expansion." (Vander's Physiology, 10th Edition)

c. Two things can *activate* a lymphatic leukocyte.

i. Direct contact with an antigen through immunoglobulin (antibody) receptor engagement for B cells or contact with antigen presented by Antigen Presenting Cells on MHC for T cells

ii. Detection of lymphokines (cytokines or proteins produced by by activated helper T cells. *Note*: Activation here refers to a process whereby an antigen sends an extracellular signal telling recipient cells (stem or progenitor cells) to proliferate and/or differentiate—a.k.a. "make a cell fate decision." Activation in other contexts can mean activation of a signaling pathway that elicits a nuclear and/or cellular response (such as antigen/T cell receptor binding which elicits proliferation and attack), or activation of particular feedback loops, neural circuits, and body systems.

2) Differentiation:

a. Location-secondary lymphoid organs such as lymph nodes and spleen

b. After activation, B cell progeny differentiate to create plasma cells or memory B cells. **Plasma cells** produce *massive* amounts of clonal **antibodies** which are specific to the activating antigen. When bound to their targets, antibodies recruit and guide other molecules and cells to perform the actual attack. Antibodies themselves can attack: when bound to antigens, antibodies clump together and deactivate foreign molecules without needing a cell around to help. Antibodies also recruit Natural Killer cells, monocytes, and eosinophils which participate in Antibodydependent Cell-mediated Cytotoxicity (for more info see http://www.ncbi.nlm.nih.gov/books/bv.fcgi?highlight=ADCC&rid=imm.figgrp.1241)

c. Like B cells, T cells are also clonal in that if they encounter their corresponding antigen, they will proliferate to create clonal cytotoxic T cell or T helper cells that all recognize the same antigen.

3) Migration and Function

a. Location: to Secondary lymphoid organs—lymph nodes, spleen, tonsils, external body surfaces (intestinal, respiratory, urinary reproductive)

b.. Function: **T Lymphocytes** play a major role in clearing infections. When a **helper T cell** is activated by binding to an antigen/MHC protein macrophage or other antigen-presenting cell, this T lymphocyte releases **lymphokines**. The lymphokine molecules signal proliferation, can activate other immune cells like B cells and NK cells, and can also aid in the activation of **cytotoxic T cells** so they can poke holes in the membranes of enemy cells then secrete toxins that dissolve them.

c. Once the attack is successfully completed, the great majority of the B cells,

plasma cells, helper T cells, and cytotoxic T cells die by **apoptosis**.

4) Memory

a. Memory B and T cells are leftover from the initial activation/proliferation phase, but lymphokines also stimulate the production of local/tissue memory T and memory B lymphocytes, from which quiescent B and T more quickly respond—with *greater numbers* of activated mature B and T cells—the same pathogen next time it enters the body.

DISEASES OF THE IMMUNE SYSTEM AND BLOOD

HIV/AIDS

Acquired immunodeficiency syndrome (AIDS) is a disease caused by the human immunodeficiency virus. HIV is a retrovirus of the lentivirus family. This disease is so devastating because it selectively destroys T cells, particularly T helper cells, thereby making its hosts immunodeficient.

Some causes of HIV infection are:

a) Having sex with someone infected with HIV
b) Through exposure to infected blood such as via tainted blood transfusion
c) Exposure to HIV before or during birth, including breastfeeding.

Symptoms of HIV include: Rapid weight loss; dry cough; recurring fever and profuse night sweats; profound and unexplained fatigue; swollen lymph glands in the armpits, groin, or neck; diarrhea that lasts for more than a week; white spots/unusual blemishes on the tongue, mouth, or throat; pneumonia; red, brown, pink, or purplish blotches on or under the skin; memory loss, depression, and other neurological disorders.

In 1993, the CDC expanded their definition of AIDS to include all HIV positive people with a $CD4_+$ T cell count below 200 per µL of blood or 14% of all lymphocytes. Because the immune systems of patients with AIDS lack a functional attack mechanism, they usually succumb to opportunistic
infections that are easily treatable in healthy people. In 1990, the World Health Organization (WHO) grouped these infections and conditions together by introducing a staging system for patients infected with HIV-1. An update took place in September 2005.

 Stage I: HIV infection is asymptomatic and not categorized as AIDS
 Stage II: includes minor mucocutaneous manifestations and recurrent upper respiratory tract infections
 Stage III: includes unexplained chronic diarrhea for longer than a month, severe bacterial infections and pulmonary tuberculosis
 Stage IV: includes toxoplasmosis of the brain, candidiasis of the esophagus, trachea,

bronchi or lungs and Kaposi's sarcoma; these diseases are indicators of AIDS.

LEUKEMIA
Leukemia is cancer of your body's blood-forming tissues, including your bone marrow and lymphatic system. It usually starts in your white blood cells. Your white blood cells are potent infection fighters— they normally grow and divide in an orderly way, as your body needs them. But in leukemia, your bone marrow produces a large number of abnormal white blood cells, which don't function properly.

Symptoms of leukemia include: Weakness, feeling tired, weight loss, fever, night sweats, enlarged lymph nodes (felt as lumps under the skin), pain or a sense of "fullness" in the belly, excess bruising,bleeding, frequent or severe nosebleeds, and bleeding gums.

LYMPHOMA
Lymphoma is cancer that originates in your lymphatic system, the disease-fighting network spread throughout your body. Tumors develop from lymphocytes — a type of white blood cell. In one type of lymphoma, cells in the lymphatic system grow abnormally and may spread beyond the lymphatic system.

Symptoms of lymphoma include: Sometimes no symptoms besides lumps under or near skin and cough or trouble breathing. Other symptoms include: night sweats, weight loss, fever, itching, tiredness, and poor appetite. Symptoms depend on location in body; there may be swollen tender areas or personality changes if in brain.

SICKLE CELL ANEMIA
Sickle cell anemia is an inherited form of anemia — a condition in which there aren't enough healthy red blood cells to carry adequate oxygen throughout your body. Normally, your red blood cells are flexible and round, moving easily through your blood vessels. In sickle cell anemia, the red blood cells become rigid, sticky and are shaped like sickles or crescent moons. These irregularly shaped cells can get stuck in small blood vessels, which can slow or block blood flow and oxygen to parts of the body.

Symptoms of sickle cell anemia include: Sickle cell causes anemia (lack of red blood cells). The sickle-shaped cells get caught in capillaries and also block the flow of blood through vessels, resulting in lung tissue damage, pain episodes, and stroke. It also causes damage to the spleen, kidneys and liver. The damage to the spleen makes patients easily overwhelmed by bacterial infections.

HEMATOPOIETIC STEM CELL TREATMENTS

For some cases of leukemia and lymphoma, bone marrow transplants can cure the patient. Bone marrow samples are purified to enrich with hematopoietic stem cells and some mesenchymal stem cells. After the patient receives chemotherapy to destroy existing bone marrow cells, the transplant is infused intravenously. The cells find their way to the bone marrow and repopulate the body with healthy cells. Bone marrow transplants may offer a cure in a small number of sickle cell anemia cases. Researchers continue to look for new treatments for the disease. These include gene therapy, improved bone marrow transplants, and umbilical cord blood transplants

Sources of bone marrow

The best source of bone marrow is from healthy, genetically compatible sibling donors (or the patient's own cord blood saved from birth). Bone marrow is aspirated from the pelvic bone or other large bone, and the stem cells are purified from the sample.

Umbilical cord transplant

Patients may also receive umbilical cord and peripheral blood transplants (containing hematopoietic stem cells) in addition to bone marrow transplants. Since the patient's own peripheral blood contains stem cells with an identical HLA, there is no risk of rejection with peripheral blood transplants. Hematopoietic stem cells from the umbilical cord seem to be less immunogenic than those found in bone marrow, and may be quite useful in treating leukemia, lymphoma, and sickle cell anemia.

Finding a match: Major Histocompatibility Complex

Because your immune cells can recognize foreign antigens, if you introduce cells from someone else, they will be seen as "foreign" by your immune system and this will result in an attack on the introduced tissues. Human Leukocyte Antigen (HLA) is the MHC for humans. Inherited from your parents, HLAs differ in type and must be present in the right combination in order for your immune cells to leave your own body's tissues alone. The combination of HLAs that your tissues express is different from blood type, which is determined by the sugar residues on the surface of your red blood cells. The best matches for transplants would have identical or nearly identical HLAs to the patient, and this means treatments developed to avoid rejection must be individualized. Another possibility is to deliver something along with the transplant that would protect it from the immune system.

Challenges to overcome

The immune system with its ability to recognize and destroy foreign substances in the body poses a significant challenge for stem cell medicine using cells from an allogeneic source. Any transplant must be **histocompatible** and the patient is given immunosuppressive drugs to avoid the rejection of stem cell transplants even if the donor is well-matched to the patient. Instead of immune suppression, drugs that stimulate **immune tolerance** to specific antigens could make transplants

more successful. What if there was a way to get around the immune system—to create cells or tissues from embryonic or adult stem cells that couldn't be recognized? Induced Pluripotent Stem cell technologies—where a skin or other somatic cell is genetically engineered into a pluripotent stem cell—are potential ways to bypass immune rejection since the cells originate from the patient and would be completely histocompatible. iPS cells will be discussed in the iPS cell unit (coming soon). Another strategy is to develop drugs that induce immune tolerance. You and your students can learn more about immune tolerance here: http://www.immunetolerance.org/public/about-us/whatimmune-tolerance. The National Institutes of Health funds "Antigen-specific tolerance induction [that] is a major goal for the treatment or prevention of autoimmune disease and graft rejection, which are currently controlled by nonspecific, immunosuppressive therapies. Immunosuppression results in increased rates of infections, cancers and drug-related pathology. Other applications of tolerance induction include allergies and asthma, bone marrow replacement, and future gene therapy for a large number of human diseases. A greater understanding of **tolerogenic** processes is also needed to enhance vaccine development, in order to prevent pathogen-induced tolerance during immunization" (NIH, 1997). California is now funding stem-cell-related lab and clinical research in these promising areas of research and medicine. Watch a video by CIRM-funded researcher Dr. Jeffrey Bluestone, who talks about the possibility of priming stem cell transplants for immune tolerance before they are transplanted to limit the use of immunosuppressive drugs on the patient:
http://www.cirm.ca.gov/Videos_Basics_JeffreyBluestone

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